

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1-11. (Canceled)

12. (Currently amended) A method for identifying an agent that interacts with an active site of a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE) binding protein or peptide, the method comprising:

~~providing a crystalline composition comprising Beta-site APP Cleaving Enzyme (BACE);~~

~~determining the providing a three dimensional structure of a complex of BACE and an APP inhibitor, wherein:~~

- (i) BACE comprises the amino acid sequence of residues 58-447 of SEQ ID NO:1,
- (ii) the APP inhibitor comprises the sequence SEVNStaVAEF, wherein Sta is (S)-statine; and
- (iii) the three dimensional structure of the complex comprises the relative structural coordinates according to Figures 1A-1EEE of amino acids LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAI370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391,

THR392, VAL393, GLY395, ALA396 and ILE447, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å;  
generating a three dimensional model of the three dimensional structure of the complex an active site of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of amino acids SER71, GLY72, LEU91, ASP93, GLY95, SER96, VAL130, PRO131, TYR132, THR133, GLN134, ILE171, ILE179, ILE187, ALA188, ARG189, PRO190, TRP258, TYR259, ASP284, LYS285, ASP289, GLY291, THR292, THR293, ASN294, ARG296 and ARG368, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å;  
performing computer fitting analysis of a candidate agent with the three dimensional model of the complex; and  
identifying an the agent, using the three dimensional model.

13. (Original) The method of Claim 12, wherein the ± root mean square deviation from the backbone atoms of said amino acids is not more than 1.0 Å.

14. (Original) The method of Claim 12, wherein the ± a root mean square deviation from the backbone atoms of said amino acids is not more than 0.5 Å.

15. (Currently amended) The method of Claim 12, wherein the agent is identified by performing computer fitting analysis comprises determining the degree of association between of the candidate agent and with the three dimensional model of the complex.

16. (Previously presented) The method of Claim 12, further comprising contacting the agent with BACE in order to determine the effect the agent has on BACE.

17. (Canceled)

18. (Currently amended) The method of Claim 16, wherein the agent is a potential inhibitor of binding between BACE and APP or an APP peptide.

19. (Currently amended) The method of Claim 18, further comprising contacting the agent with BACE in the presence of APP or the APP peptide.

20. (Currently amended) A method for identifying an agent that interacts with an active site of a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE) binding protein or peptide, the method comprising:

providing a crystalline composition comprising BACE;

determining the providing a three dimensional structure of BACE, wherein BACE consists essentially of the amino acid sequence of residues 58-447 of SEQ ID NO:1, and wherein the three dimensional structure comprises the relative structural coordinates of BACE according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å;

generating a three dimensional model of an active site of the three dimensional structure of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of amino acids LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396 and ILE447, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å;

performing computer fitting analysis of a candidate agent with the three dimensional model of BACE; and

identifying an the agent, using the three dimensional model.

21. (Previously presented) The method of Claim 20, wherein the  $\pm$  a root mean square deviation from the backbone atoms of said amino acids is not more than 1.0 Å.

22. (Original) The method of Claim 20, wherein the  $\pm$  a root mean square deviation from the backbone atoms of said amino acids is not more than 0.5 Å.

23. (Currently amended) The method of Claim 20, wherein the agent is identified by performing computer fitting analysis comprises determining the degree of association between of the candidate agent and with the three dimensional model of BACE.

24. (Previously presented) The method of claim 20, further comprising contacting the agent with BACE in order to determine the effect the agent has on BACE.

25. (Canceled)

26. (Currently amended) The method of Claim 24, wherein the agent is a potential inhibitor of binding between BACE and APP or an APP peptide.

27. (Currently amended) The method of Claim 26, further comprising contacting the agent with BACE in the presence of APP or an APP peptide.

28-32. (Canceled)

33. (Previously presented) The method of claim 35, wherein obtaining the agent comprises synthesizing the agent.

34. (Previously presented) The method of claim 36, wherein obtaining the agent comprises synthesizing the agent.

35. (Previously presented) The method of claim 12, further comprising obtaining the agent.

36. (Previously presented) The method of claim 20, further comprising obtaining the agent.

37. (New) The method of claim 12, wherein the three dimensional model of the complex comprises the relative structural coordinates of BACE of Figures 1A-1EEE,  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

38. (New) The method of claim 20, wherein the three dimensional structure of BACE further comprises the structural coordinates of an APP inhibitor.

39. (New) The method of claim 38, wherein the APP inhibitor comprises the sequence SEVNStaVAEF, wherein Sta is (S)-Statine.

40. (New) The method of claim 19, wherein the APP peptide comprises the sequence SEVNStaVAEF, wherein Sta is (S)-Statine.

41. (New) The method of claim 27, wherein the APP peptide comprises the sequence SEVNStaVAEF, wherein Sta is (S)-Statine.

42. (New) The method of claim 12, further comprising providing a crystalline composition of the complex, wherein the crystalline composition has space group I222, and unit cell parameters  $a=86.627$ ,  $b=130.861$ ,  $c=130.729$ , and  $\alpha=\beta=\gamma=90^\circ$ .

43. (New) The method of claim 12, further comprising providing a crystalline composition of BACE, wherein the crystalline composition has space group I222, and unit cell parameters  $a=86.627$ ,  $b=130.861$ ,  $c=130.729$ , and  $\alpha=\beta=\gamma=90^\circ$ .